Clinical trial results:
A phase II, open label, non-randomised, single centre, clinical trial of ANX776 in Healthy Volunteers and patients with Glaucoma, Age-Related Macular Degeneration, and Optic Neuritis and Down's Syndrome

Summary

EudraCT number	2016-002531-15
Trial protocol	GB
Global end of trial date	07 June 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	15/0959

Additional study identifiers

ISRCTN number	ISRCTN10751859
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Comprehensive Clinical Trials Unit at UCL
Sponsor organisation address	Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk
Scientific contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2018
Global end of trial reached?	Yes
Global end of trial date	07 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary outcome is the efficacy of the intervention ascertained by the DARC Count, which is the number of apoptosing retinal cells visualised 4 hours after the ANX776 injection in patients with Glaucoma, Age-related Macular Degeneration (AMD), Optic Neuritis (ON), Down's syndrome and in Healthy volunteers.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

The following protocol pre-defined reasons for stopping the trial early for a participant were in place: unacceptable toxicity or adverse event; inter-current illness that prevents further treatment; any change in the participant’s condition that in the clinician’s opinion justifies the discontinuation of the trial.

Participants were under no obligation to enter the trial and they could withdraw consent or assent / withdrawal of consent by the legal representative for Down’s syndrome participants at any time during the trial, without having to give a reason, and without their clinical care being affected.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	08 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 113
Worldwide total number of subjects	113
EEA total number of subjects	113

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	78
From 65 to 84 years	31
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Participants for the glaucoma, AMD, optic neuritis and healthy volunteer groups were recruited through designated participant identification centres and REC approved advertisements. Participants in the Down's syndrome arm were recruited from two pre-existing cohorts in the Cambridge Intellectual and Developmental Disabilities Research Group.

Pre-assignment

Screening details:

Eligibility criteria for all groups were those aged 18 years or above, with clear optical media in the studied eye, refractive error not higher than spherical equivalent of 10 D and women of childbearing potential identified as not pregnant. Each subgroup was enrolled into the study in accordance with group-specific inclusion/ exclusion criteria.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Glaucoma

Arm description:

Subjects with at least one eye with a diagnosis of Glaucoma.

Arm type	Experimental
Investigational medicinal product name	ANX776
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg

Arm title	Age-related Macular Degeneration

Arm description:

Subjects with Age-related Macular Degeneration (AMD).

Arm type	Experimental
Investigational medicinal product name	ANX776
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg

Arm title	Optic Neuritis

Arm description:

Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.

Arm type	Experimental

Investigational medicinal product name	ANX776
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg

Arm title	Down's Syndrome

Arm description:

Subjects with confirmation of Down's Syndrome.

Arm type	Experimental
Investigational medicinal product name	ANX776
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg

Arm title	Healthy Volunteers

Arm description:

Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.

Arm type	Active comparator
Investigational medicinal product name	ANX776
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4mg

Number of subjects in period 1	Glaucoma	Age-related Macular Degeneration	Optic Neuritis
Started	20	19	18
Completed	20	19	14
Not completed	0	0	4
Ineligible	-	-	4
Missing baseline spot count	-	-	-

Number of subjects in period 1	Down's Syndrome	Healthy Volunteers
Started	16	40
Completed	15	39
Not completed	1	1
Ineligible	-	1
Missing baseline spot count	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Glaucoma
Reporting group description:	
Subjects with at least one eye with a diagnosis of Glaucoma.	
Reporting group title	Age-related Macular Degeneration
Reporting group description:	
Subjects with Age-related Macular Degeneration (AMD).	
Reporting group title	Optic Neuritis
Reporting group description:	
Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.	
Reporting group title	Down's Syndrome
Reporting group description:	
Subjects with confirmation of Down's Syndrome.	
Reporting group title	Healthy Volunteers
Reporting group description:	
Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.	

Reporting group values	Glaucoma	Age-related Macular Degeneration	Optic Neuritis
Number of subjects	20	19	18
Age categorical Units: Subjects			
Adults (18-64 years)	12	1	13
From 65-84 years	8	14	1
85 years and over	0	4	0
Ineligible participant	0	0	4
Age continuous Units: years			
arithmetic mean	61.1	79.9	45.3
standard deviation	± 13.7	± 7.4	± 12.1
Gender categorical Units: Subjects			
Female	6	9	11
Male	14	10	3
Ineligible participant	0	0	4
Ethnicity Units: Subjects			
Caucasian	16	15	10
Black	3	0	1
Asian	0	4	1
Hispanic	0	0	1
Other	1	0	1
Ineligible participant	0	0	4
AMD type Units: Subjects			
Early AMD & Late AMD	0	1	0

Early AMD & Neovascular AMD	0	1	0
Late AMD	0	3	0
Neovascular AMD	0	12	0
Early AMD	0	2	0
Not applicable	20	0	18
Glaucoma category			
Units: Subjects			
Glaucoma	8	0	0
Glaucoma suspect	12	0	0
Not applicable	0	19	18
Weight			
Units: Kg			
arithmetic mean	81.3	65.8	74.8
standard deviation	± 17.5	± 9.9	± 14.3
BMI			
Units: kg/m^2			
arithmetic mean	26.8	24.9	26.1
standard deviation	± 4.6	± 3.1	± 4.7
SBP			
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	140	142	132
standard deviation	± 17.0	± 17.5	± 18.7
DBP			
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	77.9	71.4	73.6
standard deviation	± 10.3	± 9.6	± 18.7
Heart rate			
Units: beat/min			
arithmetic mean	69.5	64.9	69.0
standard deviation	± 14.0	± 9.7	± 11.3
Respiratory rate			
Units: breaths/min			
arithmetic mean	17.0	16.6	16.9
standard deviation	± 2.6	± 1.4	± 1.9
Autofluorescence spot count			
Units: Baseline spot count			
geometric mean	30.2	67.5	30.8
standard deviation	± 1.62	± 1.71	± 1.39
IOP			
Mean intraocular pressure of eligible eyes.			
Units: mmHg			
arithmetic mean	18.9	13.5	13.9
standard deviation	± 2.6	± 3.5	± 2.0
Corneal pachymetry			
Units: micrometer			
arithmetic mean	555	541	528
standard deviation	± 33.6	± 37.2	± 40.3
VF mean deviation			
Visual field mean deviation			
Units: dB			

arithmetic mean	-1.7	0	-4.7
standard deviation	± 2.1	± 0	± 5.7
Visual acuity			
Units: logmar			
arithmetic mean	0.01	0.45	-0.00000001
standard deviation	± 0.08	± 0.9	± 0.28

Reporting group values	Down's Syndrome	Healthy Volunteers	Total
Number of subjects	16	40	113
Age categorical			
Units: Subjects			
Adults (18-64 years)	16	31	73
From 65-84 years	0	8	31
85 years and over	0	0	4
Ineligible participant	0	1	5
Age continuous			
Units: years			
arithmetic mean	39.7	47.6	
standard deviation	± 7.7	± 17.1	-
Gender categorical			
Units: Subjects			
Female	4	21	51
Male	12	18	57
Ineligible participant	0	1	5
Ethnicity			
Units: Subjects			
Caucasian	16	28	85
Black	0	3	7
Asian	0	6	11
Hispanic	0	2	3
Other	0	0	2
Ineligible participant	0	1	5
AMD type			
Units: Subjects			
Early AMD & Late AMD	0	0	1
Early AMD & Neovascular AMD	0	0	1
Late AMD	0	0	3
Neovascular AMD	0	0	12
Early AMD	0	0	2
Not applicable	16	40	94
Glaucoma category			
Units: Subjects			
Glaucoma	0	0	8
Glaucoma suspect	0	0	12
Not applicable	16	40	93
Weight			
Units: Kg			
arithmetic mean	71.8	70.0	
standard deviation	± 18.7	± 11.6	-
BMI			
Units: kg/m^2			

arithmetic mean	29.7	24.0	
standard deviation	± 5.7	± 3.3	-
SBP			
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	119	129	
standard deviation	± 15.3	± 14.5	-
DBP			
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	70.4	75.8	
standard deviation	± 8.9	± 9.0	-
Heart rate			
Units: beat/min			
arithmetic mean	65.3	69.7	
standard deviation	± 11.1	± 9.9	-
Respiratory rate			
Units: breaths/min			
arithmetic mean	17.3	16.7	
standard deviation	± 1.2	± 1.9	-
Autofluorescence spot count			
Units: Baseline spot count			
geometric mean	22.6	30.2	
standard deviation	± 1.32	± 1.34	-
IOP			
Mean intraocular pressure of eligible eyes.			
Units: mmHg			
arithmetic mean	0	13.6	
standard deviation	± 0	± 2.5	-
Corneal pachymetry			
Units: micrometer			
arithmetic mean	0	530	
standard deviation	± 0	± 25.8	-
VF mean deviation			
Visual field mean deviation			
Units: dB			
arithmetic mean	0	-0.3	
standard deviation	± 0	± 1.1	-
Visual acuity			
Units: logmar			
arithmetic mean	0	-0.03	
standard deviation	± 0	± 0.1	-

End points

End points reporting groups

Reporting group title	Glaucoma
Reporting group description:	
Subjects with at least one eye with a diagnosis of Glaucoma.	
Reporting group title	Age-related Macular Degeneration
Reporting group description:	
Subjects with Age-related Macular Degeneration (AMD).	
Reporting group title	Optic Neuritis
Reporting group description:	
Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.	
Reporting group title	Down's Syndrome
Reporting group description:	
Subjects with confirmation of Down's Syndrome.	
Reporting group title	Healthy Volunteers
Reporting group description:	
Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Only those participants who met the eligibility criteria and were not recruited by mistake are included in the analyses.	

Primary: Primary outcome

End point title	Primary outcome
End point description:	
Raw DARC counts are taken from imaging of each eligible eye using an automated process built on an algorithm which was developed blind to disease group to ensure an objective measure which is comparable across groups. The cSLO images were background subtracted and standardised before a template matching approach was applied using a 50*50 pixel 'ideal spot' template to identify spot candidates. Once identified, spot candidates will be extracted from each cSLO image and spot morphology recorded. An exploratory technique was undertaken to validate an algorithm for differentiating 'true' DARC spots amongst candidates. The resulting DARC spots were summed for each eye to yield a 'weighted' DARC count. Analysis will be repeated using the 'weighted' DARC count produced using the algorithm as exploratory outcome.	
End point type	Primary
End point timeframe:	
4 hours post injection.	

End point values	Glaucoma	Age-related Macular Degeneration	Optic Neuritis	Down's Syndrome
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20[1]	19[2]	14[3]	15[4]
Units: raw DARC counts				
geometric mean (confidence interval	42.0 (38.4 to	76.0 (63.5 to	37.1 (29.2 to	30.0 (26.2 to

95%)	45.9)	91.0)	47.1)	34.2)

Notes:

[1] - Analysis based on the 38 eligible eyes.

[2] - Analysis based on the 32 eligible eyes.

[3] - Analysis based on the 22 eligible eyes.

[4] - Analysis based on the 30 eligible eyes.

End point values	Healthy Volunteers			
Subject group type	Reporting group			
Number of subjects analysed	39[5]			
Units: raw DARC counts				
geometric mean (confidence interval 95%)	46.3 (41.7 to 51.4)			

Notes:

[5] - Analysis based on the 75 eligible eyes.

Statistical analyses

Statistical analysis title	Glaucoma and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 4 hours post injection.

Comparison groups	Glaucoma v Healthy Volunteers
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.1

Statistical analysis title	AMD and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between AMD participants and Healthy volunteers at 4 hours post injection.

Comparison groups	Age-related Macular Degeneration v Healthy Volunteers
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.27

Statistical analysis title	ON and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between ON participants and Healthy volunteers at 4 hours post injection.

Comparison groups	Optic Neuritis v Healthy Volunteers
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.02

Statistical analysis title	Down's syndrome and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between Down's syndrome participants and Healthy volunteers at 4 hours post injection.

Comparison groups	Down's Syndrome v Healthy Volunteers
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	0.98

Secondary: Secondary outcome - 2 hours post injection

End point title	Secondary outcome - 2 hours post injection

End point description:

Comparison of raw DARC counts between each of the study groups and Healthy volunteers at 2 hours post injection.

End point type	Secondary

End point timeframe:

2 hours post injection.

End point values	Glaucoma	Age-related Macular Degeneration	Optic Neuritis	Down's Syndrome
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20[6]	19[7]	14[8]	15[9]
Units: Raw DARC count				
geometric mean (confidence interval 95%)	41.3 (36.6 to 46.5)	72.9 (59.9 to 88.8)	48.4 (41.4 to 56.5)	29.9 (26.5 to 33.8)

Notes:

[6] - Analysis based on the 38 eligible eyes.

[7] - Analysis based on the 32 eligible eyes.

[8] - Analysis based on the 22 eligible eyes.

[9] - Analysis based on the 30 eligible eyes.

End point values	Healthy Volunteers			
Subject group type	Reporting group			
Number of subjects analysed	39[10]			
Units: Raw DARC count				
geometric mean (confidence interval 95%)	47.0 (42.6 to 52.0)			

Notes:

[10] - Analysis based on the 75 eligible eyes.

Statistical analyses

Statistical analysis title	Glaucoma and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 2 hours post injection.

Comparison groups	Glaucoma v Healthy Volunteers
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.06

Statistical analysis title	AMD and Healthy Volunteers

Statistical analysis description:	
Comparison of raw DARC counts between AMD group and healthy volunteers at 2 hours post injection.	
Comparison groups	Age-related Macular Degeneration v Healthy Volunteers
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.27

Statistical analysis title	ON and Healthy Volunteers
Statistical analysis description:	
Comparison of raw DARC counts between ON group and healthy volunteers at 2 hours post injection.	
Comparison groups	Optic Neuritis v Healthy Volunteers
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.09

Statistical analysis title	Down's syndrome and Healthy Volunteers
Statistical analysis description:	
Comparison of raw DARC counts between Down's syndrome group and healthy volunteers at 2 hours post injection.	
Comparison groups	Down's Syndrome v Healthy Volunteers
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	0.96

Secondary: Secondary outcome - 15 minutes post injection

End point title	Secondary outcome - 15 minutes post injection

End point description:

Comparison of raw DARC counts between each study group and healthy volunteers at 15 minutes post injection.

End point type	Secondary

End point timeframe:

15 minutes post injection.

End point values	Glaucoma	Age-related Macular Degeneration	Optic Neuritis	Down's Syndrome
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20[11]	19[12]	14[13]	15[14]
Units: raw DARC count				
geometric mean (confidence interval 95%)	33.3 (29.9 to 37.1)	67.9 (57.2 to 80.6)	35.9 (30.7 to 42.0)	27.6 (24.8 to 30.7)

Notes:

[11] - Analysis based on the 38 eligible eyes.

[12] - Analysis based on the 32 eligible eyes.

[13] - Analysis based on the 22 eligible eyes.

[14] - Analysis based on the 30 eligible eyes.

End point values	Healthy Volunteers			
Subject group type	Reporting group			
Number of subjects analysed	39[15]			
Units: raw DARC count				
geometric mean (confidence interval 95%)	32.3 (28.9 to 36.1)			

Notes:

[15] - Analysis based on the 75 eligible eyes.

Statistical analyses

Statistical analysis title	Glaucoma and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 15 minutes post injection.

Comparison groups	Glaucoma v Healthy Volunteers
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.38

Statistical analysis title	AMD and Healthy Volunteers
Statistical analysis description:	
Comparison of raw DARC counts between AMD group and healthy volunteers at 15 minutes post injection	
Comparison groups	Age-related Macular Degeneration v Healthy Volunteers
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.49

Statistical analysis title	ON and Healthy Volunteers
Statistical analysis description:	
Comparison of raw DARC counts between ON group and healthy volunteers at 15 minutes post injection	
Comparison groups	Optic Neuritis v Healthy Volunteers
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.15

Statistical analysis title	Down's syndrome and Healthy Volunteers
Statistical analysis description:	
Comparison of raw DARC counts between Down's syndrome group and healthy volunteers at 15 minutes post injection.	
Comparison groups	Down's Syndrome v Healthy Volunteers

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.07

Other pre-specified: Exploratory analysis - weighted DARC counts

End point title	Exploratory analysis - weighted DARC counts[16]

End point description:

An exploratory technique was undertaken to validate an algorithm for differentiating 'true' DARC spots amongst candidates. Spot candidate populations were gated to exclude non-DARC spot objects and artefacts based on spot area (> 10 pixels and < 1000 pixels in size), standard deviation (standardised intensity units > 0.5) and solidity (measure of roundness/ overall concavity) < 0.75). The resulting DARC spots were summed for each eye to yield a 'weighted' DARC count.

End point type	Other pre-specified

End point timeframe:

2 hours post injection

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: At present, data are available for the Glaucoma participants and Healthy volunteers only. The same technique will be used to obtain the weighted DARC counts in all the other groups.

End point values	Glaucoma	Healthy Volunteers		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[17]	22[18]		
Units: weighted DARC count				
geometric mean (confidence interval 95%)	131.4 (97.0 to 177.9)	98.3 (78.6 to 123.1)		

Notes:

[17] - Analysis based on images of 32 eligible eyes having clear quality for intensity measurements.

[18] - Analysis based on images of 41 eligible eyes having clear quality for intensity measurements.

Statistical analyses

Statistical analysis title	Glaucoma and Healthy Volunteers

Statistical analysis description:

Comparison of weighted DARC counts between Glaucoma group and healthy volunteers at 2 hours post injection.

Comparison groups	Glaucoma v Healthy Volunteers

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants (or carer for Down’s syndrome participants) were followed up via telephone call 30 days after administration of IMP to check for any symptoms and/or adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Glaucoma

Reporting group description:

Subjects with at least one eye with a diagnosis of Glaucoma.

Reporting group title	Age-related Macular Degeneration

Reporting group description:

Subjects with Age-related Macular Degeneration (AMD).

Reporting group title	Optic Neuritis

Reporting group description:

Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.

Reporting group title	Down's Syndrome

Reporting group description:

Subjects with confirmation of Down's Syndrome. All results including baseline data are based on the 15 patients with complete baseline data.

Reporting group title	Healthy Volunteers

Reporting group description:

Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.

Serious adverse events	Glaucoma	Age-related Macular Degeneration	Optic Neuritis
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Down's Syndrome	Healthy Volunteers	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Glaucoma	Age-related Macular Degeneration	Optic Neuritis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	4 / 18 (22.22%)
Nervous system disorders			
Feeling disorientated			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
General disorders and administration site conditions			
Exhaustion/ Lethargy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Rash on canula site			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Sore throat			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Problems with balance			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye disorders			
Deteriorating eyesight			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Difficulty seeing objects in motion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Sensitivity to light			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Tired eyes			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Swollen feet			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Down's Syndrome	Healthy Volunteers	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	3 / 40 (7.50%)	
Nervous system disorders			
Feeling disorientated			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Exhaustion/ Lethargy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Rash on canula site			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Sore throat			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			

Problems with balance			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Deteriorating eyesight			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Difficulty seeing objects in motion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	
Sensitivity to light			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Tired eyes			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Swollen feet			
subjects affected / exposed	0 / 16 (0.00%)	0 / 40 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2016	Protocol updated to v3.0 with the following: removal of the Down's syndrome group and a reduction of the sample size accordingly by 20; general participant exclusion criterion in relation to contraception and pregnancy amended for consistency; inclusion of a table of additional pre-clinical data for DARC; clarifications throughout.
03 January 2017	Extension of the expiry date of the IMP (ANX776) until 30 June 2017 based on new stability testing data. Updated IMPD.
20 April 2017	Protocol updated to v4.0 with the following: re-inclusion of a subgroup of 20 participants with Down's syndrome. This subgroup was originally approved by the MHRA but was removed as the REC requested further scientific and ethical rationale for the inclusion of this subgroup. The rationale is provided in the protocol.
01 June 2017	Details: Protocol updated to v9.0 with the following: REC requested changes in relation to the inclusion of the participants with Down's syndrome subgroup; general inclusion criteria edited to remove requirement for best corrected visual acuity equal to 6/24 or better at qualification and to state women of childbearing potential must agree to a pregnancy test instead of consent; removal of the exclusion criteria for age-related macular degeneration subgroup relating to the presence of ocular conditions with increased risk of choroidal neovascularisation. Only those with choroidal neovascularisation will be excluded; removal of the single exclusion criteria for the optic neuritis subgroup; clarifications throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported